REMARKS

Claims 1-4, 6, 8, 12-16, 19-21, 23-24, 26, 29-33, 36-40, 43-44, 112, 114, 118-125, 128, 131-133 and 135-138 are pending in the present application. Claims 5, 7, 9-11, 17-18, 22, 25, 27-28, 34-35, 41-42, 45-111, 113, 115-117, 126-127, 129-130 and 134 have been cancelled without prejudice or disclaimer.

Claims 1-2, 6, 8, 12-13, 15-16, 19-21, 23, 30, 112 and 114 have been amended. Support for these amendments appears throughout the specification and claims as originally filed. No new matter has been added. Applicants, by amending any claims herein and/or canceling any claims, make no admission as to the validity of any rejection made by the Examiner against any of these claims. Applicants reserve the right to reassert any of the claims canceled herein or the original claim scope of any claim amended herein, in a continuing application.

Specifically, claims 1, 21, 30 and 112 have been amended to recite, in part, "...wherein when the co-solvent comprises propylene glycol, the propylene glycol is present in an amount of less than 10% by weight...." These claims have also been amended to recite, in part, "one or more penetration agents selected from the group consisting of dodecanol, oleyl alcohol, an amine...." Support for these amendments appears throughout the specification and claims as originally filed. For example, please *see* the specification at page 3, lines 20-22, and at page 5, lines 3-4. No new matter has been added.

Claims 1, 21, 30 and 112, have been amended to recite, in part, "...optionally one or more excipients selected from the group consisting of a higher alcohol,...." Support for this amendment appears throughout the specification and claims as originally filed. For example, please *see* the specification at page 5, lines 26-27. No new matter has been added.

In addition, claim 30 has been amended to recite, in part, "...optionally one or more excipients selected from the group consisting of a higher alcohol, a vitamin, a preservative, a buffer, a stabilizer, a propellant, a hair generating agent, an antibacterial agent, a refrigerant, an amino acid, an oil component, a perfume, an antioxidant, a UV absorber, a dye, a humectant, a thickener, a gelling agent, and a color additive,..." Support for this amendment appears throughout the specification and claims as originally filed. For example, please *see* the specification at pages 4-5; page 4, line 15; and page 5, lines 26-27. No new matter has been added.

Claims 2, 6, 8, 12-13, 15-16, 19-20, 23 and 114 have been amended to place them in proper U.S. format. No new matter has been added.

In view of the following, further and favorable consideration is respectfully requested.

I. At page 2 of the Official Action, the Examiner has rejected claims 1, 21 and 112 under 35 USC § 112, second paragraph as being indefinite.

The Examiner asserts that "The claims are indefinite because they comprise an improper Markush group citing optionally one or more excipients...The Markush

group is improper because the species belonging to the group do not possess a commonality."

In view of the following, this rejection is respectfully traversed.

MPEP § 2173.05(I) recites the following:

> The materials set forth in the Markush group ordinarily must belong to a recognized physical or chemical class or to an art-recognized class. However, when the Markush group occurs in a claim reciting a process or ***a combination*** (not a single compound), it is sufficient if the members of the group are disclosed in the specification to ***possess at least one property in common which is mainly responsible for their function in the claimed relationship***, and it is clear from their very nature or from the prior art that all of them possess this property... ***Where a Markush expression is applied only to a portion of a chemical compound, the propriety of the grouping is determined by a consideration of the compound as a whole, and does not depend on there being a community of properties in the members of the Markush expression.*** (emphasis added)

See also MPEP § 803.02.

In the present case, the recited excipients possess at least ***one*** property in common which is mainly responsible for ***their function in the claimed relationship***. The property that they have in common is that they are all excipients and all function as excipients in the claimed relationship. Further, the claims in question are composition and method claims where the Markush expression is applied to only a portion of the claimed subject matter, where the propriety of the grouping is determined by a consideration of the claimed subject matter as a whole. Here, regardless of the selected excipient, the compositions all include minoxidil and are effective for treating hair loss. Accordingly, the propriety of the Markush

grouping does not depend on there being a community of properties in the members of the Markush expression. *See* MPEP § 2173.05(I).

In view of the foregoing, it is submitted that claims 1, 21 and 112 are clear and definite within the meaning of 35 USC § 112, second paragraph. Accordingly, the Examiner is respectfully requested to withdraw this rejection as to claims 1, 21, and 112.

II. At page 3 of the final Official Action, the Examiner has maintained the rejection of claims 1-4, 6, 8, 12, 13, 15-16, 19-21, 23-24, 26, 29, 112, 114, 118-125, 128, 131-132 and 135-138 under 35 USC § 103 (a), as being unpatentable over Peck et al. in view of Weiner et al. or Yu et al., respectively.

The Examiner asserts that "It would have been obvious to the skilled artisan to combine the teachings of Peck et al. and Weiner and utilize the instant minoxidil acid salt" because Weiner teaches that this addition yields a hydrophilic compound that allows for better penetration into the hair follicles.

Regarding Applicants previous arguments and the submitted rule 132 Declaration, the Examiner asserts that the arguments and Declaration are not persuasive. The Examiner maintains her position that Weiner shows that the addition of an acid salt yields a hydrophilic compound and allows for better penetration into the hair follicles.

With regard to Yu et al., the Examiner asserts that Yu et al. teach that adding lactic acid dissolves minoxidil, providing better penetration of minoxidil.

With regard to claims 1 and 112, the Examiner also asserts that while the claims were amended to recite the transition language "consisting of," they were also amended to optionally include one or more excipients that would allow for the inclusion of lipid vesicles which would be considered an excipient, i.e., a penetration agent.

In view of the following, this rejection is respectfully traversed.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court very recently held in *KSR International Co. v. Teleflex Inc. et al.*, 550 U.S. 398 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR*, 550 U.S. at 417) Second, the proposed modification of the

prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

With regard to motivation to combine references, **MPEP 2143** discusses the requirements of a *prima facie* case of obviousness. First, there must be some suggestion or motivation to combine the reference teachings or to modify the reference, and second, there must be a reasonable expectation of success. Finally, the prior art reference or references when properly combined, must teach or suggest all the claim limitations.

Regarding motivation to modify properly combined references, **MPEP 2143.01** states that a proposed modification cannot render the prior art unsatisfactory for its intended purpose. If it does, then there is no suggestion or motivation to make the proposed modification. Further, the proposed modification cannot change the principle operation of a reference.

Regarding *teaching away*, **MPEP 2141.02** states that prior art must be considered in its entirety, including disclosures that *teach away* from the claims. See also **MPEP 2145(X)(D)**. The Federal Circuit in *Takeda v. Alphapharm* found that the prior art taught away from the closest compound because the prior art in fact disclosed a broad selection of compounds where the closest prior art

compound exhibited negative properties that would have led the skilled artisan away from that compound.

In *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F. 3d 1350 (Fed. Cir. 2007), the Federal Circuit rejected Alphapharm's argument that the prior art would have led one of ordinary skill in the art to select compound b as a lead compound most promising to modify in order to improve its antidiabetic activity and thus potentially arrive at the claimed pioglitazone. The district court considered three references in reaching its determination, namely Takeda's '200 patent; Sodha II; and Takeda's '779 patent. The district court found that Sodha II taught away from compound b and that any suggestion in the '779 patent to select compound b was essentially negated by the disclosure of Sodha II in view of the more exhaustive and reliable scientific analysis presented by Sodha II and the teaching away. Accordingly, the Federal Circuit accorded more weight to the Sodha II reference.

A. The Claims

Present claims 1, 21 and 112 have been amended, in part, to recite "optionally one or more excipients selected from the group consisting of a higher alcohol, vitamin, a preservative, a buffer, a stabilizer, a propellant, a hair generating agent, an antibacterial agent, a refrigerant, an amino acid, an oil component, a perfume, an antioxidant, a UV absorber, a dye, a humectant, a thickener, a gelling agent, a perfume and a color additive." More specifically, claims 1, 21 and 112 clearly exclude the inclusion of a lipid vesicle. In contrast, a lipid vesicle is clearly

required by Weiner et al. Weiner et al., in the Summary of the Invention, states that the invention is "based, in part, on the discovery that making a material...and encapsulating the drug in a lipid vesicle, can improve delivery. This is particulary pertinent to the delivery of minoxidil." *See also* Weiner et al. the claims.

B. Peck et al. Does Not Qualify as an Enabling Prior Art Reference

Applicants submit that Peck et al. does not qualify as an enabling prior art reference. The relevant inquiry is ". . . whether [Peck] enabled persons skilled in this art to produce" the later invention. *See In re '318 Patent Infringement Litigation* (Fed. Cir. 2009).

In *In re '318 Patent Infringement Litigation* (Fed. Cir. 2009), a divided panel of the Federal Circuit affirmed a determination by the District Court for the District of Delaware that the claims of U.S. Patent No. 4,663,318 were invalid for lack of enablement.

Writing for the majority, Judge Dyk, joined by Judge Mayer, cited *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1358 (Fed. Cir. 1999), for the proposition that "a patent claim [that] fails to meet the utility requirement because it is not useful or operative, . . . also fails to meet the how-to-use aspect of the enablement requirement." Judge Dyk observed that "[t]ypically, patent applications claiming new methods of treatment are supported by test results," adding that "[o]ur predecessor court held in *Krimmel* [292 F.2d 948, 954 (CCPA 1961)] that animal tests showing that a new nonobvious compound 'exhibits some useful

pharmaceutical property' are sufficient to demonstrate utility" and that "under appropriate circumstances, . . . the first link in the screening chain, *in vitro* testing, may establish a practical utility for the [pharmaceutical] compound in question," citing *Cross v. Iizuka*, 753 F.2d 1040, 1051 (Fed. Cir. 1985).

In affirming the District Court's judgment of invalidity for lack of enablement, Judge Dyk stated that: "In this case, however, neither *in vitro* test results nor animal test results involving the use of galantamine to treat Alzheimer's-like conditions were provided." Judge Dyk stated that "at the end of the day, the specification, even read in the light of the knowledge of those skilled in the art, does no more than state a hypothesis and propose testing to determine the accuracy of that hypothesis," which is "not sufficient."

Judge Dyk, therefore, concluded that "[t]he '318 patent's description of using galantamine to treat Alzheimer's disease thus does not satisfy the enablement requirement because the '318 patent's application did not establish utility."

In the present case, Peck et al. broadly describe at page 2 a composition (1) that includes 1 to about 5% minoxidil and 10 to about 50% propylene glycol. Thereafter, Peck et al. describe specific formulations, for example, formulations (e) and (f) at page 4, that each include 50% propylene glycol and 5% minoxidil. Further, each of Examples 5 and 6 of Peck et al. describe preparing compositions including 5% minoxidil and 50% propylene glycol.

The formulations of Peck et al. that include a high concentration of minoxidil, i.e., 5%, also include high concentrations of propylene glycol, i.e., 50%. *See* formulations (e) and (f), and Examples 5 and 6, of Peck et al.

Moreover, all of the examples of Peck et al. have very ***high levels*** of propylene glycol or other diols and triols. Please *see* the above discussion of Peck et al.

Peck et al. describe a composition that includes 1 to about 5% minoxidil and 10 to about 50% propylene glycol. Peck et al. do ***not*** describe or exemplify a composition containing ***both*** at least 5% minoxidil and less than 10% propylene glycol. Rather, Peck et al. at most may hypothetically or theoretically suggest a composition containing both at least 5% minoxidil and less than 10% propylene glycol for treating hair loss, with no testing to determine the accuracy of that hypothesis. Accordingly, the description in Peck et al. of a composition that includes 1 to about 5% minoxidil and 10 to about 50% propylene glycol does not satisfy the enablement requirement because the Peck et al. specification does not establish utility of the presently claimed composition, i.e., at least 5% minoxidil and less than 10% propylene glycol. *See In re '318 Patent Infringement Litigation* (Fed. Cir. 2009) discussed above.

Accordingly, Applicants submit that Peck et al. does not qualify as an enabling prior art reference.

C. No Prima Facie Obviousness: No Motivation to Modify and Not all Limitations Taught

(i) Not all Limitations Taught

Assuming *arguendo* that Peck et al. does qualify as an enabling prior art reference, it is submitted that a *prima facie* case of obviousness has not been established because the Peck et al. and Weiner et al. references or the Peck et al. and Yu et al. references fail to teach or suggest all of the limitations of the claims as required by *In re Wilson*.

The Peck et al. and Weiner et al. references, or the Peck et al. and Yu et al. references, fail to teach or suggest all of the limitations of the claims as required by *In re Wilson*, because none of the foregoing references, taken alone or together, teach or suggest a composition having ***less than 10% propylene glycol.*** Further, none of the foregoing references, taken alone or together teach or suggest a composition having ***BOTH*** at least 5% minoxidil or a pharmaceutically acceptable salt thereof ***AND*** less than 10% by weight propylene glycol, as is presently claimed. Peck et al. broadly describe at page 2, composition (1) that includes 1 to about 5% minoxidil and 10 to about 50% propylene glycol. Thereafter, Peck et al. describe specific formulations, for example, formulations (e) and (f) at page 4, that each include 50% propylene glycol and 5% minoxidil. Further, each of Examples 5 and 6 of Peck et al. describe preparing compositions including 5% minoxidil and 50% propylene glycol. Peck et al. does not describe, let alone exemplify, a composition containing at least 5% minoxidil or a pharmaceutically acceptable salt thereof ***AND***

less than 10% by weight propylene glycol, as is presently claimed.

Moreover, all of the examples of Peck et al. have very ***high levels*** of propylene glycol or other diols and triols. This is conventional technology that uses high propylene glycol concentrations in order to load minoxidil into the formulation. In Example 1, where the propylene glycol amount is 20%, there is only 2% minoxidil in the formulation. In Example 2(a), where propylene glycol and butylene glycol are present in a combined amount of 40%, there is only 2% minoxidil. In Example 2 (b), where the butylene glycol amount is 15%, there is only 1% minoxidil. Likewise, in Examples 3 and 4, where the propylene glycol amount is 30%, there is only 2% minoxidil in the formulation. In Example 7, where propylene glycol and butylene glycol are present in a combined amount of 25%, there is only 2% minoxidil. Only in Examples 5 and 6 where the propylene glycol amount is 50%, is minoxidil present in an amount of 5% in the formulations. This does not teach or suggest an advantage of having ***BOTH* reduced levels** of the co-solvent such as less than 10% propylene glycol and **high loading of minoxidil** such as at least 5%, as is presently claimed. Accordingly, Peck et al. do not teach or suggest the presently claimed subject matter.

The foregoing remarks are further supported by the previously submitted Declaration (submitted with the Amendment and Response filed on November 8, 2007) under 37 CFR §1.132 by Barry Hunt ("the Hunt Declaration"). Barry Hunt is a formulation scientist of the assignee of the subject application and has been in

pharmaceutical research since 1972. He has been employed doing formulation research and development for the last 35 years.

In paragraphs 4-8, Mr. Hunt declares that he has reviewed Peck et al. and, as exemplified therein, formulations having high loading of minoxidil are accompanied by high levels of polyhydric alcohols. In fact, in paragraph 8, Mr. Hunt sets forth that Peck et al. exemplify the following formulations:

- The composition of Example 5 contains 5% minoxidil and 50% propylene glycol.
- The composition of Example 6 contains 5% minoxidil and 50% propylene glycol.
- Compositions (e) and (f) each contain 5.0% minoxidil and 50.0% propylene glycol.
- The compositions of claims 13 and 14 each contain 5.0% minoxidil and 50.0% propylene glycol.

Thus, Mr. Hunt declares in paragraph 8 that, similar to other compositions described in the prior art, the compositions exemplified in Peck et al. contain a very high percentage (i.e., 50%) of propylene glycol in order to improve the solubility of a high concentration (i.e. 5%) of minoxidil. Such high amounts of propylene glycol are not pharmaceutically or cosmetically elegant, may be unacceptable to the consumer, and may cause local irritation and hypersensitivity upon application to the scalp (*see* paragraph 6 of the Hunt Declaration).

Again, claims 1 and 112 recite the transition language "consisting of." Claim 21 recites providing a pharmaceutical composition "consisting of." This transition

language excludes components other than those expressly recited. More specifically, claims 1, 21 and 112 which recite the transition language "consisting of" and optional specific excipients, clearly exclude encapsulation in lipid vesicles.

The Examiner asserts that while the claims were amended to recite the transition language "consisting of," they were also amended to optionally include one or more excipients that would allow for the inclusion of lipid vesicles which would be considered an excipient, i.e., a penetration agent.

Applicants strongly disagree with the Examiner's assertion. None of claims 1, 21 or 112, recite an optional excipient that is a lipid vesicle. The recited optional excipients neither include a lipid vesicle nor allow for the inclusion of a lipid vesicle.

Further, by the above statement, the Examiner admits that a lipid vesicle is a penetration agent. Claims 1, 21, 30 and 112 all recite a composition "consisting of" the recited components. All of these claims recite an optional penetration agent selected from the recited group. The recited penetration agents ***do not include a lipid vesicle***. Accordingly, assuming *arguendo* that recited members of the optional excipients could form a penetration agent, i.e., a lipid vesicle, such a lipid vesicle is excluded from the claims because it does not fall within the recited penetration agents.

With regard to Yu et al., Yu et al. do not cure the deficiencies of Peck et al. because Yu et al also do not teach or suggest a composition having ***BOTH*** at least 5% minoxidil or a pharmaceutically acceptable salt thereof ***AND*** less than

approximately 10% by weight polyhydric alcohol. Yu et al. is directed to the use of hydroxyacids to enhance the "therapeutic efficacy of cosmetic and pharmaceutical agents." *See* col. 2, lines 16-21. In particular, Yu et al. describe the use of "hydroxycarboxylic acids and related compounds" as "enhancing compounds" to enhance the therapeutic efficacy of cosmetic and pharmaceutical agents in topical treatment of cosmetic conditions, dermatologic disorders, or other afflictions. *See* col. 2, lines 16-42.

Yu et al. is not concerned with and does not even remotely address the problem that the presently claimed subject matter solves, namely, increasing minoxidil amounts while minimizing amounts of propylene glycol, or other polyols. Yu et al. clearly do not describe or suggest the present composition which requires "at least 5% by weight, based on the total weight of the composition, of minoxidil or a pharmaceutically acceptable salt thereof," "an acid in an amount to substantially completely solubilize the minoxidil or a pharmaceutically acceptable salt thereof," and a co-solvent wherein when the co-solvent comprises propylene glycol, the propylene glycol is present in an amount of "less than 10% by weight."

Prophetic Example 3 of Yu et al. describe a "2% minoxidil" formulation formed by dissolving 2 grams minoxidil and 3 ml lactic acid into a mixture of 80 ml ethanol and 15 ml propylene glycol. A 2% minoxidil formulation contains much less minoxidil than the present compositions which require at least 5% minoxidil. In addition, the formulation of Example 3 of Yu et al. has a large propylene glycol

content, i.e., 15%, which amount is substantially greater than the presently claimed "less than 10% by weight."

In addition, Applicants submit that any suggestion in Yu et al. to employ a minoxidil acid salt is negated by the disclosure of Weiner et al. in view of the more exhaustive and reliable scientific analysis presented by Weiner et al. and the teaching away from the present claims by Weiner et al. *See Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., Id.*

More specifically, Weiner et al. in Examples 1-3 and in Tables 1 and 2, at pages 4-8, provide extensive comparative penetration data with regard to various encapsulated and unencapsulated minoxidil formulations. Further, as discussed herein, Weiner et al. ***teach away*** from the use of an ***unencapsulated minoxidil salt formulation***. On the other hand, Yu et al. provide ***no data at all*** with regard to minoxidil formulations. Only ***prophetic*** Example 3 of Yu et al. is directed to a composition containing a minoxidil acid salt. No data is provided. Accordingly, Weiner et al. is entitled to more weight than Yu et al. in accordance with *Takeda*. The Examiner is respectfully requested to expressly address these arguments if this rejection is to be maintained.

(ii) No Motivation to Modify

Assuming *arguendo* that Peck et al. does qualify as an enabling prior art reference, it is submitted that a *prima facie* case of obviousness has not been established because the skilled artisan would have no motivation to modify Peck et al. to incorporate the acid salt of Weiner et al. since Weiner et al. teach away from a minoxidil acid salt.

It is submitted that the skilled artisan would have no motivation to prepare a formulation by reacting minoxidil with an acid, absent encapsulation of the resultant minoxidil acid salt in a lipid vesicle, because Weiner et al. describe that an unencapsulated minoxidil salt formulation exhibits less than one-quarter the penetration exhibited by an encapsulated minoxidil acid salt formulation.

Peck et al. ***teach away*** from the presently claimed subject matter because the formulations of Peck et al. that include a high concentration of minoxidil, i.e., 5%, also include high concentrations of propylene glycol, i.e., 50%. *See* formulations (e) and (f), and Examples 5 and 6, of Peck et al. Numerous other prior art formulations also teach away from the present claims by requiring high percentages of propylene glycol or a similar diol or triol to achieve high minoxidil concentrations, i.e. greater than 5% (see the present specification at page 1, lines 11-21). **Thus, no suggestion or motivation has been provided to modify Peck et al. to arrive at the composition as recited in the present claims.**

Further, the skilled artisan would have no motivation to modify Peck et al. by

utilizing the minoxidil acid salt of Weiner et al.

In this regard, the Examiner has asserted that Weiner et al. teach modifying the solubility of the active in an aqueous solution to make it more hydrophilic which does not change the active agent's therapeutic properties, and that the modified active agent (that is more hydrophilic) has improved penetration through the hair follicle. Contrary to the Examiner's assertion, the data presented in Weiner et al. clearly illustrate that changing the solubility of minoxidil by reacting it with an acid renders the resultant formulation ***essentially undeliverable*** in the absence of encapsulation. Accordingly, not only does Weiner et al. illustrate that the resultant unencapsulated formulation does ***not*** exhibit improved penetration through the hair follicle, Weiner et al. clearly illustrate that it exhibits ***extremely poor*** penetration.

Specifically, the data presented in Example 3 of Weiner et al. shows that minoxidil reacted with lactic acid (formulation **XI**), but not encapsulated in a lipid vesicle, is essentially undeliverable into hairless rat skin. In contrast, the Weiner et al. data shows that a lipid vesicle encapsulated lactic acid-treated minoxidil (formulation **III**) penetrated living skin strata more deeply than the other tested formulations. *See* formulations **III** and **XI** in Table 1, on page 6, in the "Living skin Strata" column, and page 7, lines 9-17.

As can be seen from Table 1 of Weiner et al., the percentage of the applied dose of encapsulated minoxidil salt formulation **III** that penetrated the living skin strata was 0.75±0.33 while the percentage of unencapsulated minoxidil salt

formulation **XI** that penetrated the living skin strata was 0.18±0.01. Applicants note Weiner et al. state at page 7, line 3, that "Formula **XI** is the same as Formula **III** except lacking the vesicles." This data clearly shows that encapsulated minoxidil lactic acid salt formulation **III** had more than four times the penetration into the deepest skin strata than that of unencapsulated minoxidil lactic acid salt formulation **XI**.

Further, contrary to the Examiners assertion, Weiner et al. attribute improved penetration of the encapsulated minoxidil formulation to the lipid vesicle and the particular lipid selected and ***not*** to the minoxidil acid salt. Specifically, Weiner et al. state at page 7, lines 15-17, that "[W]hat is most interesting is that a simple change from glycerol dilaurate (C12) to glycerol disterate (C18) in the vesicle wall changes the penetration several fold."

In view of the foregoing, the skilled artisan would have no motivation to prepare a formulation by reacting minoxidil with an acid, ***absent encapsulation*** of the resultant minoxidil acid salt in a lipid vesicle, because Weiner et al. describe that ***an unencapsulated minoxidil salt formulation exhibits less than one-quarter the penetration exhibited by an encapsulated minoxidil acid salt formulation.***

In addition, Weiner et al. ***teach away*** from preparing an unencapsulated minoxidil acid salt formulation, because the skilled artisan in view of the data in Example 3 would be led away from preparing and administering an unencapsulated minoxidil salt formulation. Specifically, Example 3 of Weiner et al. illustrates that

commercial Rogaine® (formulation **XII**), which does not include a minoxidil salt, but includes minoxidil in a combination of ethanol, propylene glycol and water and is not encapsulated in a lipid vesicle, was second only to formulation **III** in efficacy (penetration of living skin strata). Again, Weiner et al. describe that the percentage of unencapsulated minoxidil salt formulation **XI** that penetrated the living skin strata was 0.18±0.01. The percentage of unencapsulated minoxidil formulation **XII** that penetrated the living skin strata was 0.35±0.14. This data clearly shows that unencapsulated minoxidil formulation **XII** had ***twice*** the penetration into the deepest skin strata than that of unencapsulated minoxidil lactic acid salt formulation **XI**. Thus, the skilled artisan in view of the data in Weiner et al., which shows that unencapsulated minoxidil formulation **XII** (commercial Rogaine®) exhibits significantly greater penetration than unencapsulated minoxidil lactic acid salt formulation **XI**, would be ***led away*** from preparing an unencapsulated minoxidil salt formulation.

In view of the foregoing, the skilled artisan would have had no motivation to prepare a formulation employing a minoxidil salt or by reacting minoxidil with an acid to form a minoxidil salt. Weiner et al. illustrate that an unencapsulated minoxidil salt formulation exhibits only half the penetration exhibited by an unencapsulated minoxidil propylene glycol formulation (commercial Rogaine®) and thus ***teaches away*** from the present claims.

In further support of the above, Applicants submit that increasing solubility is not equivalent to increasing skin permeation. Please *see* pages 28-29 of *Skin Permeation, Fundamentals and Application*, Joel L. Zatz, PhD, submitted with the Amendment and Response filed on November 8, 2007. More specifically, page 29, lines 2-4, describe that "In every case studied, the permeability coefficient of the unionized form exceeds that of the charged species, in some cases by two or three orders of magnitude."

In view of the foregoing, it is submitted that nothing in Peck et al., Weiner et al., and Yu et al., taken alone or together, renders the presently claimed subject matter obvious within the meaning of 35 USC § 103. Accordingly, the Examiner is respectfully requested to withdraw this rejection of pending claims 1-4, 6, 8, 12, 13, 15-16, 19-21, 23-24, 26, 29, 112, 114, 118-125, 128, 131-132 and 135-138.

III. At page 11 of the Official Action, the Examiner has maintained the rejection of claims 14, 30-33, 36-40, 43-44 and 133 under 35 USC § 103 (a), as being unpatentable over Peck et al. in view of Weiner et al. or Yu et al., respectively, and further in view of Uchikawa et al.

The Examiner asserts that it would have been obvious to the skilled artisan "to combine the teachings of the above references and substitute the exemplified propylene glycol with the instantly claimed glycerol and arrive at the instant invention" because "Uchikawa et al. teach both propylene glycol and glycerol are polyhydric alcohols conventionally used in the art."

In view of the following, this rejection is respectfully traversed.

Claim 14 is indirectly dependent on independent claim 1. Claims 31-33, 36-40 and 43-44 are each directly or indirectly dependent on independent claim 30. Claim 133 is indirectly dependent on independent claim 112. All of claims 1, 30 and 112 specifically exclude encapsulation in a lipid vesicle.

As discussed above in section II, incorporated herein by reference in its entirety, present claims 1 and 112 recite the transition language "consisting of." Claim 21 recites providing a pharmaceutical composition "consisting of." This transition language excludes components other than those expressly recited. In addition, claims 1, 21, 30 and 112 have been amended to recite optional specific excipients. Accordingly, claims 1, 21 and 112 clearly exclude encapsulation in lipid vesicles. *See* section II above.

In addition, it is submitted that Peck et al. does not qualify as an enabling prior art reference. Please *see* section II herein.

Further, assuming *arguendo* that Peck et al. does qualify as an enabling prior art reference, it is submitted that none of Peck et al., Weiner et al. or Yu et al., taken alone or together, teach or suggest a composition having ***BOTH*** at least 5% minoxidil or a pharmaceutically acceptable salt thereof ***AND*** less than 10% by weight propylene glycol, as presently claimed.

In addition, Weiner et al. ***teach away*** from preparing an unencapsulated minoxidil salt formulation. Please *see* the above discussions in Section II, regarding Peck et al., Weiner et al. and Yu et al., as well as the Hunt Declaration, which

arguments are hereby incorporated by reference in their entirety. Again, claims 1, 30 and 112 recite the transition language "consisting of." Claim 21 recites providing a pharmaceutical composition "consisting of." In addition, claims 1, 21, 30 and 112 have been amended to recite optional specific excipients. Accordingly, claims 1, 21, 30 and 112 clearly exclude encapsulation in lipid vesicles. *See* section II herein.

Again, Applicants submit that any suggestion in Yu et al. to employ a minoxidil acid salt is negated by the disclosure of Weiner et al. in view of the more exhaustive and reliable scientific analysis presented by Weiner et al. and the teaching away from the present claims by Weiner et al. *See Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., Id.* The Examiner is respectfully requested to expressly address this argument should this rejection be maintained.

Applicants submit that Uchikawa et al. do not cure the deficiencies of Peck et al., Weiner et al., and/or Yu et al., because Uchikawa et al. do not teach or suggest a composition having ***BOTH*** at least 5% minoxidil or a pharmaceutically acceptable salt thereof ***AND*** less than 10% by weight polyhydric alcohol, as presently claimed. Further, Uchikawa et al. do not teach or suggest employing a minoxidil acid salt.

In view of the foregoing, it is submitted that nothing in the applied references, taken alone or together, render the presently claimed subject matter obvious within the meaning of 35 USC § 103. Accordingly, the Examiner is respectfully requested to withdraw this rejection of pending claims 14, 30-33, 36-40, 43-44 and 133.

IV. At page 12 of the Official Action, the Examiner has maintained the rejection of claims 1-4, 6, 8, 12-13, 15-16, 19-21, 23-24, 26, 112, 118-125, 128, 131-132 and 135-138 under 35 USC § 103 as being unpatentable over JP 07-048230 in view of Weiner et al. or Yu et al. and further in view of Caldini et al.

The Examiner asserts that it would have been obvious to the skilled artisan to combine the teachings of JP 07-048230 ("'230") and Weiner et al. or Yu et al. and utilize the instant minoxidil acid salt. The Examiner further asserts that it would have been obvious to the skilled artisan to combine the teachings of the references and utilize benzyl alcohol in the solvent system because Caldini et al. teach that the use of benzyl alcohol improves transcutaneous and transfollicular absorption of active agents.

In view of the following, this rejection is respectfully traversed.

As discussed above in section II, incorporated herein by reference in its entirety, present claims 1 and 112 recite the transition language "consisting of." Claim 21 recites providing a pharmaceutical composition "consisting of." This transition language excludes components other than those expressly recited. In addition, claims 1, 21 and 112 have been amended to recite optional specific excipients. Accordingly, claims 1, 21 and 112 clearly exclude encapsulation in lipid vesicles. *See* section II herein.

JP '230 describes a hair tonic including 0.1 to 10 g. minoxidil, 30-70 g. ethanol, and water. JP '230, as admitted by the Examiner, does not teach or suggest adding an acid or a co-solvent.

As discussed above, Weiner et al. ***teach away*** from preparing and/or administering an unencapsulated minoxidil acid salt formulation. The skilled artisan in view of Weiner et al. would have had no motivation to prepare a formulation by employing a minoxidil salt or by reacting minoxidil with an acid to form a minoxidil salt, ***absent encapsulation*** of the minoxidil salt in a lipid vesicle because Weiner et al. describe that an unencapsulated minoxidil salt exhibits extremely poor penetration. Again, the present claims do not encompass encapsulation in lipid vesicles.

Further, as discussed above, the skilled artisan would have had no motivation to prepare a formulation employing a minoxidil salt or prepare a formulation by reacting minoxidil with an acid to form a minoxidil salt, because Weiner et al. describe that commercial Rogaine® (that is unencapsulated) exhibits significantly greater penetration than exhibited by an unencapsulated minoxidil salt formulation and thus ***teach away*** from the present claims. Again, the present claims do not encompass encapsulation in lipid vesicles.

Please *see* the above remarks set forth in Section II, regarding Weiner et al. and Yu et al., incorporated herein by reference in their entirety.

With regard to Yu et al., as discussed above Yu et al. is directed to the use of hydroxyacids to enhance the "therapeutic efficacy of cosmetic and pharmaceutical agents." *See* col. 2, lines 16-21. Again, Yu et al. is not concerned with and do not even remotely address the problem that the presently claimed subject matter

solves, namely, increasing minoxidil amounts while minimizing amounts of propylene glycol, or other polyols. Yu et al. clearly do not describe or suggest the present composition which requires "at least 5% by weight, based on the total weight of the composition, of minoxidil or a pharmaceutically acceptable salt thereof," "an acid in an amount to substantially completely solubilize the minoxidil or a pharmaceutically acceptable salt thereof," and a co-solvent wherein when the co-solvent comprises propylene glycol, the propylene glycol is present in an amount of "less than 10% by weight."

Again, Applicants submit that any suggestion in Yu et al. to employ a minoxidil acid salt is negated by the disclosure of Weiner et al. in view of the more exhaustive and reliable scientific analysis presented by Weiner et al. and the teaching away from the present claims by Weiner et al. The Examiner is respectfully requested to expressly address this argument should this rejection be maintained.

Prophetic Example 3 of Yu et al. describe a "2% minoxidil" formulation formed by dissolving 2 grams minoxidil and 3 ml lactic acid into a mixture of 80 ml ethanol and 15 ml propylene glycol. A 2% minoxidil formulation contains much less minoxidil than the present compositions which require at least 5% minoxidil. In addition, the formulation of Example 3 of Yu et al. has a large propylene glycol content, i.e., 15%, which amount is substantially greater than the presently claimed "less than 10% by weight."

Regarding Caldini et al., Caldini et al. do not cure the deficiencies of JP 07-048230, Weiner et al. , and Yu et al., taken alone or together, because Caldini et al. do not teach or suggest employing a minoxidil acid salt.

In view of the foregoing, it is submitted that nothing in any of JP 07-048230, Weiner et al., Yu et al., and Caldini et al., taken alone or together, suggests the presently claimed subject matter within the meaning of 35 USC § 103. Accordingly, the Examiner is respectfully requested to withdraw this rejection of pending claims 1-4, 6, 8, 12-13, 15-16, 19-21, 23-24, 26, 112, 118-125, 128, 131-132 and 135-138.

V. At page 15 of the Official Action, the Examiner has maintained the rejection of claims 1-4, 6, 8, 12-13, 15-16, 19-21, 23-24 and 26-29 under 35 USC § 103 (a), as being unpatentable over Navarro et al. in view of Weiner et al.

The Examiner asserts that it would have been obvious to the skilled artisan "to combine the teachings of Navarro et al. and Weiner and substitute Navarro's cyclodextrin with the instant acid to convert minoxidil into a salt" because "Weiner teaches that by converting minoxidil to a hydrophilic compound, it penetrates the skin."

In view of the remarks set forth herein, this rejection is respectfully traversed.

Responsive to Applicants arguments, the Examiner asserts that claims 1 and 21 allow for the inclusion of a lipid vesicle or a cyclodextrin carrier because they recite an optional excipient which can be a lipid vesicle or a cyclodextrin carrier. More specifically, the Examiner asserts that "the cyclodextrin carrier of Weiner

[Navarro] reads on a stabilizer. As evidenced by Moldenhauer et al...compositions containing complexes of gamma-cyclodextrin and retinol or retinol derivatives have unexpected stability. Thus, Moldenhauer et al. support the examiner's argument that cyclodextrin reads on a stabilizer. As such, ...applicant's claims do not exclude Weiner's [Navarro's] cyclodextrin carrier." The Examiner also asserts that the use of cyclodextrin salt addition provides substantial penetration through the hair follicle second only to the use of a minoxidil acid salt addition. *See* the Official Action of April 15, 2009 at page 15, paragraph 4 and page 17 paragraphs 3 and 4.

Applicants strongly disagree with the Examiner's assertion that the present claims encompass a cyclodextrin carrier. None of claims 1, 21 or 112, recite an optional excipient that is a cyclodextrin carrier. The recited optional excipients neither include a cyclodextrin carrier nor allow for the inclusion of a cyclodextrin carrier.

As discussed above in section II, incorporated herein by reference in its entirety, present claim 1 recites the transition language "consisting of." Claim 21 recites providing a pharmaceutical composition "consisting of." This transition language excludes components other than those expressly recited. In addition, claims 1 and 21 have been amended to recite optional specific excipients. Accordingly, claims 1 and 21 clearly exclude encapsulation in a cyclodextrin carrier. Please *see* section II herein.

Navarro et al. describe encapsulating minoxidil in a cyclodextrin carrier, wherein cyclodextrin functions as a "host" molecule to trap the minoxidil "guest" molecule inside the ring. Navarro et al. describe the use of cyclodextrin in order to assist in the solubilization of minoxidil while avoiding high amounts of propylene glycol. Navarro et al. state the following:

> [t]he amount of γ-cyclodextrin present in the composition for hair is such that it permits a substantial reduction in the amount of solvent for minoxidil which would normally need to be added to achieve a comparable solubility of minoxidil in the absence of the aforementioned cyclodextrin. (Page 3, lines 9-13 of the English translation).

From the foregoing, it is clear that cyclodextrin is an essential element of Navarro et al. because it must be combined with minoxidil in order to impart improved solubility properties to minoxidil, thereby reducing the amount of solvent such as propylene glycol needed in the formulation. However, the present claims ***exclude*** cyclodextrin. As such, the encapsulating technique of Navarro et al. is distinguished. Please *see* section II herein.

In further support of the foregoing, the Examiner's attention is directed to the Declaration submitted previously on November 8, 2007. The Declaration under 37 CFR §1.132 by Albert Zorko Abram ("the Abram Declaration"), was filed in corresponding patent application no. 10/124,197 now US Patent No. 6,946,120, in response to a rejection of the pending claims under 35 USC § 103 as obvious in view of the disclosures of Navarro in view of Weiner et al. and further in view of Leitch.

In the Declaration, Mr. Abram declares in paragraph 9 that supplementing the teaching of Navarro with the teaching of Weiner et al. ***would destroy the intended purpose of the Navarro composition***. Mr. Abram declares in paragraph 10 that the role of cyclodextrin in Navarro is to function as a host molecule to trap the minoxidil "guest" molecule inside the ring and that it is the minoxidil-cyclodextrin "host-guest" complex that imparts improved solubility properties, as compared to a similar minoxidil composition not having cyclodextrin. Mr. Abram declares that it is recognized that cyclodextrins are unstable in acidic conditions and that subjecting cyclodextrins to acidic conditions will result in the degradation of the cyclodextrins into its individual glucose units.

Further, as discussed above and contrary to the Examiners assertion, Weiner et al. ***do not*** teach or suggest that converting minoxidil to a hydrophilic compound results in improved penetration through the hair follicle. In fact, the data in Weiner et al. clearly illustrates that a minoxidil salt formulation exhibits markedly poorer penetration as compared to the penetration exhibited by commercial Rogaine®. Accordingly, Weiner et al. ***teach away*** from the preparation/administration of an unencapsulated minoxidil salt formulation. Please *see* the above discussions in Section II with regard to Weiner et al., incorporated herein by reference in their entirety.

In view of the foregoing, it is submitted that nothing in Navarro et al. and Weiner et al., taken alone or together, renders the presently claimed subject matter

obvious within the meaning of 35 USC § 103. Accordingly, the Examiner is respectfully requested to withdraw this rejection of pending claims 1-4, 6, 8, 12-13, 15-16, 19-21, 23-24 and 26-29.

VI. At page 18 of the Official Action, the Examiner has maintained the rejection of claims 14, 30-33, 36-40, 43-44, 112, 118-125, 128 and 131-138 under 35 USC § 103 (a), as being unpatentable over Navarro et al. in view of Weiner et al. and further in view of Wong et al.

The Examiner asserts that it would have been obvious to the skilled artisan to combine the teachings of the references and further utilize a propellant because "Wong et al. teach that a propellant allows a solution to aerosolize." The Examiner further asserts that "it would have been obvious to use either propylene glycol or glycerol and arrive at the instant invention."

In view of the remarks set forth herein, this rejection is respectfully traversed.

Claim 14 is indirectly dependent on independent claim 1. Claims 31-33, 36-40 and 43-44 are each directly or indirectly dependent on independent claim 30. Claims 118-125, 128 and 131-138 are each directly or indirectly dependent on independent claim 112. All of claims 1, 30 and 112 specifically exclude encapsulation in a lipid vesicle and/or in a cyclodextrin carrier.

As discussed above in sections II and V, incorporated herein by reference in their entirety, present claims 1 and 112 recite the transition language "consisting of." Likewise, present claim 30 recites the transition language "consisting of." This transition language excludes components other than those expressly recited. In

addition, claims 1, 30 and 112 have been amended to recite optional specific excipients. Accordingly, claims 1, 30 and 112 clearly exclude encapsulation in lipid vesicles and/or in a cyclodextrin carrier. *See* sections II and V herein.

Further, as discussed above, Applicants submit that a proper case of *prima facie* obviousness has not been established. Please *see* the discussions set forth above in Sections II and V regarding each of Navarro et al. and Weiner et al., which are hereby incorporated herein by reference in their entirety. *See also* the Abram Declaration.

Applicants submit that Wong et al. do not cure the deficiencies of Navarro et al. and Weiner et al. because Wong et al. also do not teach or suggest employing a minoxidil acid salt let alone a minoxidil acid salt absent encapsulation.

In view of the foregoing, it is submitted that nothing in Navarro et al., Weiner et al., and Wong et al., taken alone or together, renders the presently claimed subject matter obvious within the meaning of 35 USC § 103. Accordingly, the Examiner is respectfully requested to withdraw this rejection of pending claims 14, 30-33, 36-40, 43-44, 112, 118-125, 128 and 131-138.

VII. At page 20 of the Official Action, claims 30-31, 36-40, 43-44, 112, 114, 118-125, 128, 131-132 and 135-138 have been rejected under 35 USC § 103 (a), as being unpatentable over Navarro et al. in view of Weiner et al. and further in view of Peck et al.

The Examiner asserts that it would have been obvious to the skilled artisan "to combine the teaching of the above references and further utilize the instant excipients."

In view of the remarks set forth herein, this rejection is traversed.

Claims 31, 36-40 and 43-44 are each directly or indirectly dependent on independent claim 30. Claims 114, 118-125, 128, 131-132 and 135-138 are each directly or indirectly dependent on independent claim 112. Claims 30 and 112 specifically exclude encapsulation in a lipid vesicle and/or in a cyclodextrin carrier.

In particular, present claims 30 and 112 recite the transition language "consisting of." Please *see* the discussions set forth above in sections II-VI incorporated herein by reference in their entirety. This transition language excludes components other than those expressly recited. In addition, claim 112 has been amended to recite optional specific excipients. Accordingly, claims 30 and 112 clearly exclude encapsulation in lipid vesicles and/or in a cyclodextrin carrier. *See* sections II and V herein.

As discussed above, Applicants submit that a proper case of *prima facie* obviousness has not been established because there is no motivation to modify Navarro et al. to incorporate the minoxidil acid salt of Weiner et al., let alone an unencapsulated minoxidil acid salt. Please *see* the discussions set forth above in

Sections II, IV and V regarding each of Navarro et al. and Weiner et al. *See also* the Abram Declaration.

Applicants submit that Peck et al. do not cure the deficiencies of Navarro et al. and Weiner et al. because Peck et al. also do not teach or suggest employing a minoxidil acid salt, let alone an unencapsulated minoxidil acid salt.

In view of the foregoing, it is submitted that nothing in any of the applied references, taken alone or together, suggest the subject matter of claims 30-31, 36-40, 43-44, 112, 114, 118-125, 128, 131-132 and 135-138 within the meaning of 35 USC § 103. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

VIII. At page 21 of the Official Action, the Examiner has rejected claims 1-4, 6, 8, 12-13, 15-16, 19-21, 23-24, 26 and 29 under 35 USC § 103 as being unpatentable over Bazzano in view of Weiner or Yu et al.

The Examiner asserts that it would have been obvious to the skilled artisan to combine the teachings of Bazzano and Weiner et al. and utilize the instant minoxidil acid salt. Alternatively, the Examiner asserts that it would have been obvious to combine the teachings of Bazzano and Yu et al. and utilize the instant acid because Yu et al. teach adding lactic acid dissolves minoxidil providing better penetration of minoxidil into the hair follicle.

In view of the following, this rejection is respectfully traversed.

Bazzano is directed to a synergistic combination of a retinoid and a minoxidil compound for topical application to the skin, hair and/or hair follicles of a mammal.

Bazzano clearly requires that the combination include a retinoid. Bazzano does not teach or suggest a combination absent a retinoid as a second active ingredient, as it describes a ***synergistic*** combination. *See* the abstract; col. 1, lines 20-30; and col. 3, lines 59-68.

The Examiner asserts that the present claims still allow for the inclusion of a lipid vesicle or a cyclodextrin carrier because they could be considered excipients. The Examiner further asserts that the retinoic acid required by Bazzano reads on the presently claimed penetration enhancer.

Claim 1 recites the transition language "consisting of." Claim 21 recites providing a pharmaceutical composition "consisting of." This transition language excludes components other than those expressly recited. More specifically, the transition language "consisting of" excludes encapsulation in lipid vesicles as well as a cyclodextrin carrier, and a retinoid. In addition, claims 1 and 21 have been amended to recite optional specific excipients. Accordingly, claims 1 and 21 clearly exclude encapsulation in a lipid vesicle and a cyclodextrin carrier, and a retinoid. Please *see* the arguments set forth in sections II-VII incorporated herein by reference in their entirety.

Applicants strongly disagree with the Examiner's assertion. None of claims 1 or 21 recite an optional excipient that is a retinoid. The recited optional excipients neither include a retinoid nor allow for the inclusion of a retinoid.

Further, the retinoid is an active in Bazzano, ***not*** an excipient.

With regard to the rejection of the claims as obvious over Bazzano in view of Weiner et al. or Yu et al., it is submitted that a *prima facie* case of obviousness has not been established because the skilled artisan would have no motivation to modify Bazzano to incorporate the minoxidil acid salt of Weiner et al. or Yu et al., let alone an unencapsulated minoxidil acid salt. Please *see* the above remarks in Sections II-VII regarding each of Weiner et al. and Yu et al., which are incorporated herein by reference in their entirety.

In view of the foregoing, it is submitted that nothing in any of the applied references, taken alone or together, suggest the subject matter of claims 1-4, 6, 8, 12-13, 15-16, 19-21, 23-24, 26 and 29 within the meaning of 35 USC § 103. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

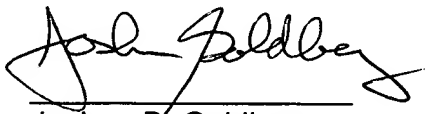
CONCLUSION

Applicants assert that the claims are in condition for immediate allowance and early notice to that effect is earnestly solicited. Should the Examiner deem that any further action by Applicants' undersigned representative is desirable and/or necessary, the Examiner is invited to telephone the undersigned at the number set forth below.

In the event this paper is not timely filed, Applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

THE NATH LAW GROUP



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